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The metabolic underpinning of eating disorders: a systematic review and meta-analysis of insulin sensitivity

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ABSTRACT

Background

A recent study reported a positive genetic correlation between anorexia nervosa and insulin sensitivity using data from genome-wide association studies. Epidemiological studies have, on the other hand, suggested that bulimia nervosa and binge-eating disorder are associated with decreased insulin sensitivity. The aim of this study was to conduct a systematic review and meta-analysis of insulin sensitivity across the spectrum of eating disorders.

Methods

EMBASE, Medline, and PsycINFO were searched for all relevant studies published until January 2017, and retrieved studies were assessed for eligibility by two independent reviewers as per predefined inclusion criteria. The associations between eating disorder subtypes and insulin sensitivity were analysed separately. Individual effect sizes were standardized, and a meta-analysis was performed to calculate a pooled effect size using random effects.

Results

Of 296 citations retrieved, 22 studies met the inclusion criteria, and 12 studies had appropriate data for meta-analysis. Using the random effects model, the pooled effect size (95% confidence interval) was 1.66 (0.79, 2.54) in people with anorexia nervosa (*n*=340) and -0.57 (-0.80, -0.34) in people with bulimia nervosa (*n*=120) and binge-eating disorders (*n*=3,241).

Interpretation

Anorexia nervosa is associated with increased insulin sensitivity whilst bulimia nervosa and binge-eating disorders are associated with decreased insulin sensitivity. The possible mechanism underpinning these findings needs to be determined.

INTRODUCTION

Many studies have reported increased insulin sensitivity during the acute phase of anorexia nervosa (AN) (Prince et al., 2009). This observation has been attributed to be a consequence of dietary restriction and weight loss leading to loss of fat mass. However, a recent study using linkage disequilibrium score regression reported a negative genetic correlation between AN and insulin resistance (r_g=−0.50, standard error (*SE*)=0.11, p=1.3×10^{-5}) (Duncan et al., 2017). This suggests that insulin sensitivity and AN share a common genetic variation. To date, there has been no study examining genetic correlations between bulimia nervosa (BN) and binge-eating disorder (BED) with metabolic traits, including insulin resistance. Clinical studies have found that both BN and BED may be associated with reduced insulin sensitivity (Raevuori et al., 2015, Mitchell, 2015). The aim of this study is to systematically examine insulin sensitivity across the spectrum of eating disorders.

RESEARCH DESIGN AND METHODS

Data sources and study selection

The following electronic libraries—EMBASE (1947 to January 2017), MEDLINE (1948 to January 2017), and PsycINFO (1806 to January 2017)—were searched to identify all relevant studies published until January 2017. The search was not restricted by language. Databases were searched using a series of logical combinations of keywords and Medical Subject Headings (MeSH) terms (Supplementary Table 1). The MeSH terms used for the article search were as follows: eating disorders, AN, BN, BED, insulin resistance, and insulin sensitivity. The titles and/or abstracts of the documents retrieved by the search strategy were screened for eligibility by two independent reviewers (AI and CK), and clearly irrelevant studies were excluded. Any disagreements were resolved through discussions and mutual dialogue. The full texts of the remaining studies were then retrieved and read in full to determine whether the predetermined inclusion criteria were met.

Inclusion/exclusion criteria

Published and unpublished studies were considered for data extraction if they met the following criteria: i) both an eating disorder and control group were present; ii) a diagnosis of either AN, BN, or BED was reported; iii) either an association between eating disorder and HOmeostasis Model Assessment of Insulin Resistance (HOMA-IR) was reported, or mean HOMA-IR values were recorded for both control and eating disorder groups. HOMA-IR is a method of assessing insulin resistance from fasting plasma insulin and fasting plasma glucose concentrations in humans and is the opposite of insulin sensitivity (Matthews et al., 1985); iv) participants were aged ≥14 years; v) the design was cross-sectional, observational, or a randomised controlled trial. Studies with samples which included patients with any type of diabetes (who were not separated from non-diabetic participants), and duplicate publications or sub-studies of included trials were not included.

Data extraction

For studies that met the inclusion criteria, data extraction was conducted using a standardised data extraction sheet and the following information (if available) was recorded: first author; year of publication; country; study design; sample size; age; sex; body mass index (BMI); eating disorder type; method of eating disorder assessment; method of insulin sensitivity assessment; and covariates adjusted for in the analysis. In instances where the full text was unavailable, corresponding authors were contacted via email.

Quality assessment

The methodological quality of the studies was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for randomised controlled trials and the Epidemiology (MOOSE) guidelines for observational studies (Moher et al., 2009, Stroup et al., 2000). Areas assessed for study quality included suitability of study design, participant

recruitment, ascertainment of eating disorders type and insulin sensitivity, and controlling of cofounders. Studies were classified as being of high quality if prospective in study design; utilised random or consecutive sampling; ascertained an eating disorder diagnosis using a structural diagnostic interview based on *Diagnostic and Statistical Manual of Mental Disorders, fourth edition or above* (DSM-IV, DSM IV-R, DSM-5) or *International Statistical Classification of Diseases and Related Health Problems 10th revision* (ICD-10) (American Psychiatric Association, 1994, American Psychiatric Association, 2000, American Psychiatric Association, 2013, World Health Organization, 1992); and accounted for confounding variables (including age, sex, physical activity, BMI, measures of adiposity, including waist circumference, waist-to-hip ratio, smoking status, alcohol consumption, socioeconomic status and educational attainment).

Primary outcome of interest

Insulin sensitivity using the HOMA-IR is the primary outcome of interest. Studies which reported mean HOMA-IR were included in both the systematic review and meta-analysis. Studies which did not report mean HOMA-IR were included in the systematic review only, as we did not have access to individual levels of fasting plasma insulin and fasting plasma glucose.

Data synthesis and meta-analysis

Analyses were conducted using the statistical package 'metafor' in the open sourced software R v3.3.3 (www.r-project.org). Given that HOMA-IR is a measure of insulin resistance which is the opposite of insulin sensitivity, effect sizes were reversed so that a positive effect size indicated increased insulin sensitivity in the clinical group. The standardized mean difference in insulin sensitivity between the clinical and control group was the primary effect size, determined using Hedges' adjusted *g* (Hedges, 1981). A fixed-effect model was deemed inappropriate as significant differences were anticipated in procedures and study populations between studies, and as such a random-effects model was performed as the basis of our analysis.

The random-effects model assumes that the heterogeneity in the differences between clinical and control groups in insulin sensitivity is purely due to random sampling. Clinical and methodological differences among the studies included in a meta-analysis may leads to statistical heterogeneity, The differences observed can be in part systematic and related to clinical study-level variables (moderators), such as BMI. Analysing the effect of potential moderators can reduce type 1 error. Both the i) mean BMI of the clinical group and ii) differences in BMI between clinical and control groups as potential moderators were therefore explored in the meta-regression analyses. In addition, eating disorder subtypes as a potential moderator were also examined in the combined analysis of BN and BED.

Publication bias

The presence of publication bias was examined by visual inspections of funnel plots (Egger et al., 1997). It was quantified statistically via Begg and Mazumdar's adjusted rank correlation and Duval and Tweedie's "trim and fill" method (Begg and Mazumdar, 1994, Duval and Tweedie, 2000). Outliers were confirmed statistically through calculation of Cook's distance (*Di*), using 1 as a cut-off. In sensitivity analyses, studies exceeding the cut-off were individually removed (starting with the study with the largest *Di*) until the funnel plot was assessed to be symmetrical. Statistical testing of effect size, heterogeneity, and publication bias were then repeated at each iteration.

Secondary analysis

Eating disorder psychopathology is closely linked to BMI and BMI is also associated with insulin sensitivity, we therefore conducted a secondary analysis examining the impact of BMI on insulin sensitivity. We first divided the studies into two subgroups depending whether both clinical and control groups were i) matched or ii) non-matched on BMI. Groups were

classified as matched if there was no significant difference in mean BMI between the clinical and control groups, with 2-tailed $p<0.05$ being deemed as significant. We then repeated the meta-analysis in the two subgroups separately. In addition, we were unable to verify whether there was any sample overlap between the three studies from Dostalova team (Dostalova et al., 2006, Dostalova et al., 2007, Dostalova et al., 2008), we therefore re-analysed the effect size of insulin sensitivity in people with AN, omitting two earlier studies from Dostalova team (Dostalova et al., 2006, Dostalova et al., 2007).

RESULTS

Study selection

The initial literature search yielded 362 records, of which 296 were unique. Of these, 117 were considered for abstract review, and 60 for full-text review. The full text was inaccessible for 1 study and 35 studies did not meet the inclusion criteria, and were therefore excluded (Figure 1). In total, 22 studies were included in the systematic review. Of the 22 records which met the inclusion criteria for systematic review, 10 studies were excluded for the meta-analysis. 8 studies were excluded because they did not have a measure of variance for mean HOMA-IR. One study was excluded because HOMA-IR was reported separately for good and poor treatment response in the AN clinical group (Yasuhara et al., 2003) and another study reported a single *F*-value with 2 degrees of freedom for the difference in HOMA-IR between the BED, subjective (i.e. non-clinical) BED, and control group, and therefore the effect size between the clinical BED and control group could not be determined (Geliebter et al., 2005). As such, 12 studies were included in the meta-analyses, one of which had data for both AN and BN and was therefore used in both analyses (Tagami et al., 2004).

Anorexia Nervosa

Thirteen studies of patients with AN were included in the systematic review, with a total of 572 participants (307 AN cases and 265 controls), all of whom were female (Table 1) (Broglio et al., 2004, Dolezalova et al., 2007, Dostalova et al., 2007, Dostalova et al., 2006, Dostalova et al., 2008, Fazeli et al., 2010, Maimoun et al., 2016, Nogueira et al., 2013, Tagami et al., 2004, Tanaka et al., 2003, Victor et al., 2015, Weinbrenner et al., 2003, Yasuhara et al., 2003). All thirteen studies were observational and used a case-control design. Total sample sizes ranged from 16 to 102 participants. Mean (SD) age of participants with AN and controls ranged from 16.5 (2.0) to 25.5 (8.1) and 15.7 (1.7) to 30.6 (8.2) respectively. Mean BMI (SD) of patients with AN and controls ranged from 13.1 (0.2) to 16.4 (1.4), and 20.3 (1.3) to 23.0 (2.8) respectively. Mean HOMA-IR (SD) was reported in ten of the thirteen studies and ranged from 0.4 (0.2) to 2.1 (0.5) in patients with AN, and 0.9 (0.2) to 3.1 (1.9) in controls. The diagnosis of AN was classified according to DSM-IV in twelve studies, and DSM-IV-TR in the remaining study.

Eight studies have the appropriate data for the primary meta-analysis (n=340) (Dolezalova et al., 2007, Dostalova et al., 2007, Dostalova et al., 2006, Dostalova et al., 2008, Maimoun et al., 2016, Nogueira et al., 2013, Tagami et al., 2004, Victor et al., 2015). A random-effects meta-analysis revealed a large pooled estimate of the mean standardized effect sizes (g=1.66; 95% CI: 0.79, 2.54; Figure 2), with the effect sizes ranging from g=0.61 to g=5.34. Heterogeneity between the studies was statistically significant (Q=35.6, $p<0.0001$) and large in magnitude (I^2=91.3%). Visual inspection of the funnel plot suggested some asymmetry, but the Begg's rank correlation test was non-significant (τ=0.214, p=0.548), and the trim and fill sensitivity method did not hypothesise any negative unpublished studies, implying an absence of publication bias. No studies had a Cook's distance exceeding the cut-off value of 1. Our moderator analysis suggests that association between AN and insulin sensitivity was moderated by BMI of the clinical group (β=-0.733; p=0.030) but not the difference in BMI between clinical and control groups (β=0.525; p=0.105). Of the eight studies included in the primary analysis, all had a statistically difference in BMI between clinical and control groups. Sensitivity analysis could not be performed. For the secondary analysis to ensure no sample overlap, data

from six studies (*n*=289) was used and random-effects meta-analysis revealed a large pooled estimate of the mean standardized effect sizes (*g*=1.57; 95% CI: 0.39, 2.74).

Bulimia Nervosa and Binge-Eating Disorder

Seven studies of patients with BN were included in the systematic review with a total of 301 participants (145 BN cases and 156 controls), all of whom were female (Table 1) (Bello et al., 2010, Dynesen et al., 2008, Karountzos et al., 2016, Kojima et al., 2005, Pijl et al., 1995, Tagami et al., 2004, Yasuhara et al., 2004). Five studies were observational and used a case-control design, and two were randomised controlled trials in BN. Total sample sizes ranged from 21 to 99 participants. Mean (SD) age of participants with BN and controls ranged from 21.5 (3.4) to 27.7 (5.7), and 23.0 (2.4) to 32.3 (8.7) respectively. Mean BMI (SD) of patients with BN and controls ranged from 19.8 (2.1) to 22.0 (2.2), and 20.3 (1.5) to 23.1 (2.7) respectively. Mean HOMA-IR (SD) was reported in three of the seven studies, and ranged from 1.0 (6.0) to 2.6 (1.4) in patients with BN, and 0.3 (0.5) to 2.0 (1.0) in controls. The diagnosis of BN was classified according to DSM-IV in five studies, DSM-III in one study, and was not stated in the remaining study.

Three studies of patients with BED were included in the systematic review with a total of 3264 participants (191 BED cases and 3,073 controls), of which 1759 were female (Table 1) (Abraham et al., 2014, Geliebter et al., 2005, Succurro et al., 2015). All three studies were observational: two studies used a cross-sectional design and one study used a case-control design. Total sample sizes ranged from 23 to 3126 participants. Mean (SD) age of patients with BED and controls ranged from 29.0 (8.4) to 47.0 (9.3), and 33.1 (8.7) to 46.5 (9.1), respectively. Mean BMI (SD) of participants with BED and controls ranged from 33.0 (7.0) to 43.7 (6.8), and 27.5 (5.4) to 37.2 (6.2) respectively. Mean HOMA-IR (SD) was reported in two of the three studies, and ranged from 3.4 (2.5) to 11.6 (22.7) in patients with BED, and 2.2 (1.7) to 4.9 (3.1) in controls. The diagnosis of BED was classified according to DSM-IV in all studies.

For the primary meta-analysis, three studies have appropriate data for BN (*n*=120) (Pijl et al., 1995, Tagami et al., 2004, Yasuhara et al., 2004) and two for BED (*n*=3,241) (Abraham et al., 2014, Succurro et al., 2015).. Given the small number of studies available for BN and BED, we therefore conducted a combined meta-analysis of exploratory nature. A random-effects meta-analysis revealed a moderate pooled estimate of the mean standardized effect sizes (*g*=-0.57; 95% CI: -0.80, -0.34; Figure 3). Two of the three BN studies showed a non-significant effect size whereas all BED studies showed a significant negative effect size.

Heterogeneity between the studies was statistically non-significant (Q=6.07, p=0.194) and small in magnitude (I^2=27.8%). I^2 is however subject to bias where the number of studies in the meta-analysis is small (Von Hippel, 2015) and thus, I^2 should be interpreted with caution. Visual inspection of the funnel plot did not suggest publication bias. The rank correlation test was also non-significant (τ=0.400, p=0.483) and the trim and fill sensitivity method did not hypothesis any unpublished. No study had a Cook's distance exceeding the cut-off value of 1. Neither moderator analysis nor secondary analysis was conducted given the small number of studies available.

Risk of bias and strength of evidence

The primary strength of our meta-analysis is that reporting was complete for the majority of the studies. Mean BMI and age of participants were reported in all studies except one study of AN (Dolezalova et al., 2007). All case-control studies reported matching for controls on age, except for two studies of AN (Broglio et al., 2004, Nogueira et al., 2013) and two studies of BN (Pijl et al., 1995, Yasuhara et al., 2004). However, other important confounding factors such as BMI and waist circumference were

not controlled for, as they were integral to the diagnosis, especially for AN. In addition, sample sizes of each individual studies were generally small and of the 22 studies included in the systematic review, only 12 studies reported appropriate mean HOMA-IR for the meta-analysis, further reducing the sample sizes. Moreover, eating disorder diagnoses were only confirmed in 7 of the 22 studies using structured interview, with only 5 of these naming the interview used. The overall risk of bias was therefore medium to high.

DISCUSSION

Main findings

To our knowledge this is the first systematic review and meta-analysis which has been conducted to examine the association between eating disorders and insulin sensitivity. The main findings of this study were that i) a positive, statistically significant association exists between AN and increased insulin sensitivity; and ii) a negative, statistically significant association exists between BN/BED and insulin sensitivity. The findings in people with BN/BED is exploratory and should be interpreted with caution, given that the small number of studies currently available. In addition, the impact of BMI on the associations with AN and BN/BED could not be fully explored as there was no study with BMI-matched clinical and control groups for AN and a paucity of studies for BN and BED. In addition, our analysis suggests that association between AN and insulin sensitivity was moderated by BMI of the clinical group. Therefore, BMI as a potential confounder of the associations remain unclear at present. One possible way to circumvent the effect of BMI is to examine insulin sensitivity in people who have recovered from or possibly at high risk of developing AN and BED.

Limitations

The study has several limitations which need to be considered when interpreting our findings. Firstly, most studies included in this review utilised cross-sectional or case-control study designs. Thus, one cannot directly infer a causal link between eating disorder subtypes and insulin sensitivity. Secondly, insulin sensitivity was measured using HOMA-IR in this meta-analysis but other methods to measure insulin sensitivity are available. For example, the gold standard is a hyperinsulinemic-euglycemic clamp. However, it involves greater participant burden and can be unsuitable for large-scale cross-sectional studies due to logistic requirements and repeated sampling. In addition, a strong correlation has been demonstrated between HOMA-IR and the hyperinsulinemic-euglycemic clamp in the healthy population (r=0.88, p<0.0001) (Matthews et al., 1985). Thirdly, HOMA-IR applies a bio-mathematical model and the potential impact of severe underweight as present in AN on the accuracy of the measurement is unclear. The exact BMI range in which the use of HOMA-IR is valid has not yet been established [personal communication with HOMA developers], and thus it cannot be ruled out that the HOMA-IR method may be invalid in people with AN. Fourthly, it has been suggested that asymmetry testing is only appropriate if i) I^2<50% with non-significant Q, ii) a maximal-to-minimal ratio variance across studies is greater than 4, and iii) a minimum of 10 studies are analysed, with statistically significance in at least one study (Ioannidis and Trikalinos, 2007). Using these guidelines, the absence of publication bias determined through statistical testing for each analysis may not be meaningful given that all analyses violated these criteria. Fifthly, we were unable to explore the impact of AN-subtypes, namely AN-restricting type and AN-binge eating/purging type, on insulin sensitivity, given the data available. Lastly, the studies included in this systematic review for AN and BN consist only of females and thus, the generalisability of our findings for males with AN or BN remain unknown.

Interpretation

A possible explanation of our findings is that insulin sensitivity may have an impact on appetite regulation via central nervous system. Insulin receptors are expressed at the dopaminergic neurons within the ventral tegmental area (VTA) of the midbrain (Volkow and Wise, 2005). The VTA region is part of the reward circuitry and involved in food seeking behaviours, providing a

possible mechanism for insulin to influence the motivation-reward pathways, contributing to the development or maintenance of eating disorders. This explanation is currently speculative and further investigations are needed to disentangle the metabolic mechanism underpinning eating disorders.

Implications

This study adds weight to the notion that insulin sensitivity may be involved in the aetiology of eating disorders. To confirm our findings, more studies are needed to examine the associations of BN/BED and insulin sensitivity. Furthermore, the comparison between recovered patients and healthy controls may shed light on the relationship between eating disorders and insulin sensitivity. Conducting genome-wide association studies in both BN and BED and subsequently examining their genetic correlations with metabolic traits, such as insulin sensitivity, could also be an informative basis for future research investigating the metabolic underpinnings of eating disorders. Adopting a more experimental approach by measuring changes in glucose pre- and post-meals in people with different types of eating disorders might also clarify the underlying mechanisms.

CONCLUSION

This systematic review and meta-analysis further supports the notion that AN is associated with increased insulin sensitivity. Our findings also tentatively suggest that BN and BED are associated with decreased insulin sensitivity. However, we could not rule out whether the alterations in insulin sensitivity are sequelae of or prerequisite to an eating disorder. Altered glucose homeostasis appears to be present across the spectrum of eating disorders, with potential implications for treatment and risk prediction.

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Table 1. Summary table of studies included in the systemic review

Author	Year	Country	Study type	ED diagnostic tool (classification)	Sample (n) [ED] [HC]	Female (%) [ED] [HC]	Age, Mean (SD) [ED] [HC]	BMI, Mean (SD) [ED] [HC]	HOMA-IR, Mean (SD) [ED] [HC]
ANOREXIA NERVOSA									
Broglio[a]	2004	The Netherlands	Case-control	NA (DSM IV)	9 7	100 100	24·2 (5.4) 30·6 (8.2)	14·7 (1.2) 20·3 (1.3)	NA
Dolezalova	2007	Czech Republic	Case-control	Clinical evaluation (DSM IV)	12 18	100 100	NA	16.4 (1.4) 23.0 (2.8)	2.0 (0.6) 3.0 (1.9)
Dostalova[b]	2006	Czech Republic	Case-control	Detailed psychiatric evaluation (DSM IV)	13 16	100 100	23.4 (5.0) 24.1 (4.8)	15.2 (1.9) 21.2 (1.3)	0.8 (1.1) 2.8 (1.5)
Dostalova[b]	2007	Czech Republic	Case-control	Detailed psychiatric evaluation (DSM IV)	10 12	100 100	24.4 (5.0) 23.3 (4.5)	15.4 (1.9) 20.9 (2.4)	0.4 (0.2) 0.9 (0.2)
Dostalova	2008	Czech Republic	Cross-sectional, case-control	Mini-International Neuropsychiatric Interview (DSM IV)	17 17	100 100	25.0 (5.5) 24.7 (2.4)	15.9 (1.4) 22.9 (1.7)	2.1 (0.5) 2.8 (1.3)
Fazeli[a]	2010	USA	Cross-sectional, case-control	Interview (DSM IV)	11 12	100 100	16.5 (2.0) 15.7 (1.7)	16.4 (1.0) 22.2 (3.5)	NA
Maïmoun	2016	France	Cross-sectional, case-control	NA (DSM IV)	50 50	100 100	18.0 (2.1) 18.1 (2.7)	15.7 (1.8) 21.1 (2.2)	0.9 (0.7) 2.2 (0.9)
Nogueira	2013	France	Case-control	NA (DSM IV)	11 10	100 100	21.9 (1.2) 24.6 (0.5)	13.1 (0.2) 22.3 (0.5)	0.5 (0.2) 1.5 (0.2)
Tagami[c]	2004	Japan	Case-control	NA (DSM IV)	31 13	100 100	25.5 (8.1) 25.7 (2.9)	14.0 (2.5) 20.3 (1.5)	1.0 (1.2) 2.0 (1.0)

Author	Year	Country	Study Type	ED diagnostic tool (classification)	Sample (n) [ED] [HC]	Female (%) [ED] [HC]	Age, Mean (SD) [ED] [HC]	BMI, Mean (SD) [ED] [HC]	HOMA-IR, Mean (SD) [ED] [HC]
ANOREXIA NERVOSA *(continued)*									
Tanaka[a]	2003	Japan	Case-control	NA	20	100	19.6 (4.5)	13.5 (1.4)	NA
				(DSM IV)	10	100	21.0 (1.9)	21.4 (1.3)	
Victor	2015	Spain	Cross-sectional, case-control	NA	24	100	22.4 (6.8)	16.3 (1.6)	0.7 (0.5)
				(DSM IV-TR)	36	100	24.3 (3.4)	20.9 (1.4)	1.4 (0.5)
Weinbrenner[a]	2003	Germany	Case-control	NA	51	100	24.2 (7.1)	15.2 (1.4)	NA
				(DSM IV)	51	100	25.5 (6.4)	22.1 (1.4)	
Yasuhara[a^]	2003	Japan	Case-control	Structured interview	48	100	23.5 (5.0)	13.5 (1.8)	NA
				(DSM IV)	13	100	23.8 (1.8)	20.9 (1.0)	
BULIMIA NERVOSA									
Bello[a]	2010	USA	Randomised controlled trial	NA	10	100	23.8 (4.6)	21.9 (1.8)	NA
				(DSM IV)	11	100	24.8 (6.5)	23.1 (2.7)	
Dynesen[a]	2008	Denmark	Case-control	Structured interview	19	100	24 .0 (4.2)	21.5 (3.3)	NA
				(DSM IV)	20	100	23.0 (2.4)	21.4 (2.8)	
Karountzos[a]	2016	Canada	Case-control	NA	32	100	NA	NA	NA
				(NA)	67	100			
Kojima[a]	2005	Japan	Case-control	NA	10	100	24.7 (4.7)	20.0 (1.9)	NA
				(DSM IV)	12	100	24.8 (2.8)	20.2 (1.7)	
Pijl	1995	The Netherlands	Randomised controlled trial	NA	15	100	27.7 (5.7)	22.0 (2.2)	1.2 (1.2)
				(DSM III)	19	100	32.3 (8.7)	22.5 (1.9)	0.3 (0.5)
Tagami[c]	2004	Japan	Case-control	NA	11	100	23.5 (3.9)	20.5 (1.8)	2.6 (1.4)
				(DSM IV)	13	100	25.7 (2.9)	20.3 (1.5)	2.0 (1.0)

Author	Year	Country	Study Type	ED diagnostic tool (classification)	Sample (n) [ED] [HC]	Female (%) [ED] [HC]	Age, Mean (SD) [ED] [HC]	BMI, Mean (SD) [ED] [HC]	HOMA-IR, Mean (SD) [ED] [HC]
BULIMIA NERVOSA *(continued)*									
Yasuhara	2004	Japan	Case-control	Mini-International Neuropsychiatric Interview (DSM IV)	48 14	100 100	21.5 (3.4) 23.1 (1.5)	19.8 (2.1) 21.5 (1.1)	1.0 (0.6) 1.1 (0.5)
BINGE EATING DISORDERS									
Abraham[d]	2014	USA	Cross-sectional	Questionnaire on Eating and Weight Patterns-Revised (DSM IV)	150 2976	52.9 51.8	47.0 (9.3) 46.5 (9.1)	33.0 (7.0) 27.5 (5.4)	3.4 (2.5) 2.2 (1.7)
Geliebter[a]	2005	USA	Case-control	Questionnaire on Eating and Weight Patterns & Clinical Interview (DSM IV)	11 12	100 100	29.0 (8.4) 33.1 (8.7)	36.6 (6.2) 35.3 (5.5)	NA
Succurro	2015	Italy	Cross-sectional	Structured interview (DSM IV)	30 85	73.3 62.4	36.8 (12.7) 41.8 (12.8)	43.7 (6.8) 37.2 (6.2)	11.6 (22.7) 4.9 (3.1)

[a] Not included in meta-analysis.

[b] Excluded from the secondary analysis of the meta-analysis to ensure that there is no sample overlap.

[c] The study examined both AN and BN clinical groups. The control group is the same for both AN and BN clinical groups.

[d] HOMA-IR analyses exclude participants with diabetes. Baseline characteristics include individuals with diabetes (*n*=172 for BED group, *n*=3,127 for HC group)

n: number of subjects; ED: eating disorders; HC: healthy controls; SD: standard deviation; BMI: body mass index; HOMA-IR: Homeostatic Model assessment-insulin resistance; NA: not available; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, third edition.

Figure 1. Flow chart of studies included in systematic review and meta-analysis

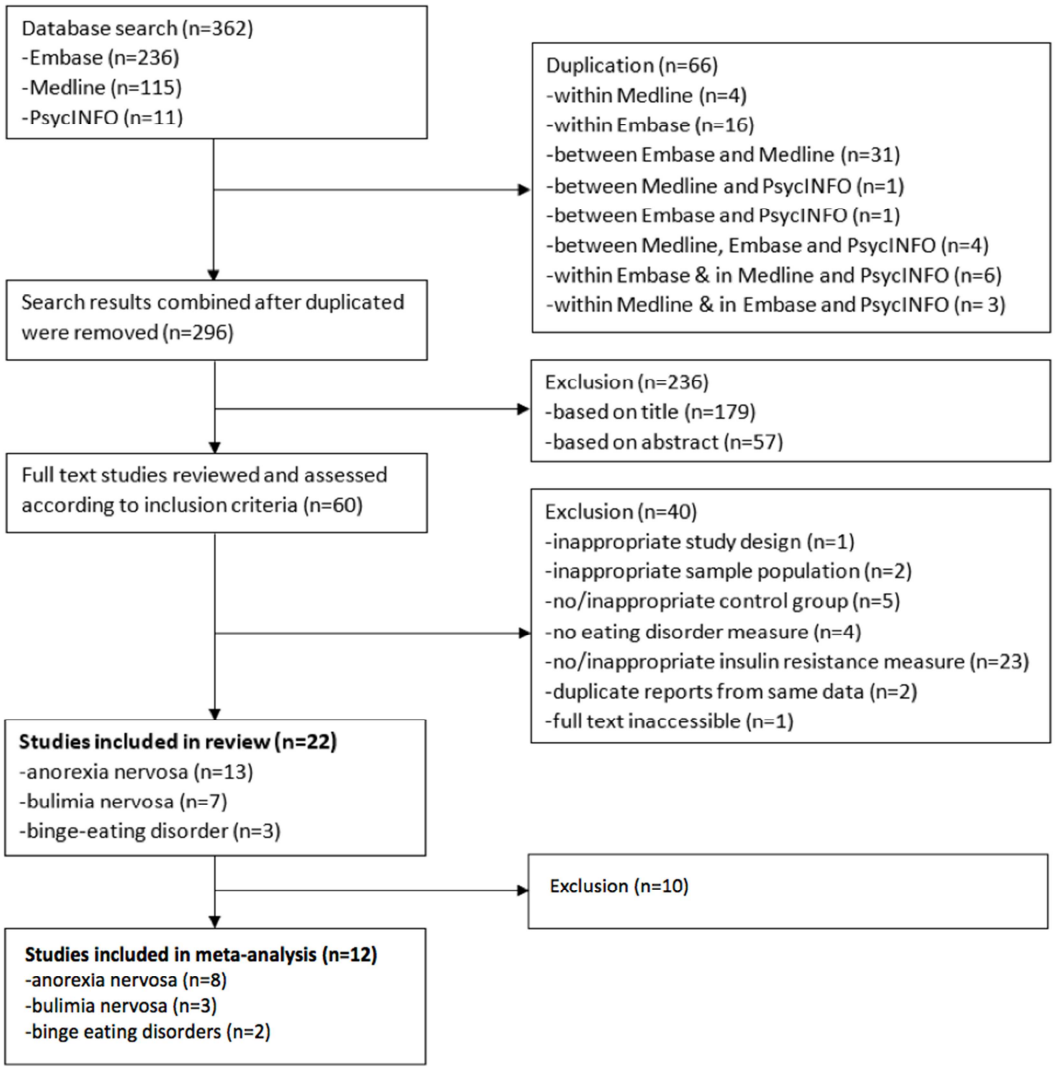

Figure 2. Insulin sensitivity in patients with anorexia nervosa and controls.

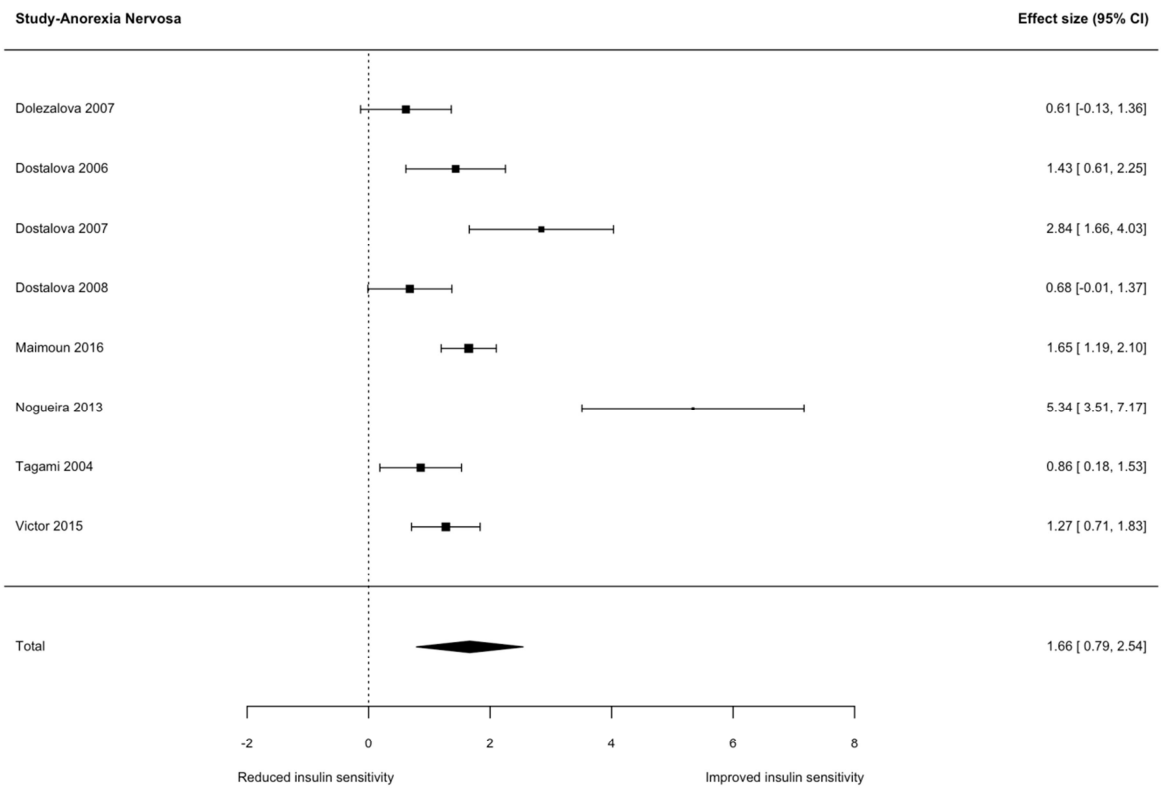

Figure 3. Insulin sensitivity in patients with bulimia nervosa/binge-eating disorders and controls.